Vaccines and Related Biological Products Advisory Committee Meeting
December 15, 2005

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FDA / CBER / OVRR

ZOSTAVAX™ Overview

- Proposed indication
- Introduction / background
- ZOSTAVAX™ clinical development
- Protocol 004 review
- Protocol 009 review
- Summary
- Questions / Discussion

ZOSTAVAX™ Proposed Indication

- Prevention of herpes zoster (shingles)
- Prevention of postherpetic neuralgia (PHN)
- Reduction of acute and chronic zoster-associated pain as measured by the burden of illness (BOI) score developed by the sponsor
- In individuals 50 years of age or older

Varicella Zoster Virus

- Persists in sensory nerve ganglia
- Reactivation associated with aging, immunosuppression
- Pruritic, vesicular rash - localized or diffuse
- Hospitalization ~3/1,000
- Death ~1/60,000

Herpes Zoster (HZ) Complications

- Neurologic
  - Postherpetic neuralgia
  - Ocular
  - Encephalitis
  - Cranial and peripheral nerve palsies
- Visceral
  - Pneumonia (adults)
  - Hepatitis
- Bacterial infection
  - Superinfection of skin and underlying structures
  - Bacterial pneumonia
  - Septicemia, toxic shock syndrome

Postherpetic Neuralgia (PHN)

- PHN usually resolves within a few weeks, but in some cases severe, debilitating pain and paresthesia may persist for a year or more
- Pain control may be inadequate in more severe or protracted cases

VZV Epidemiology - 1

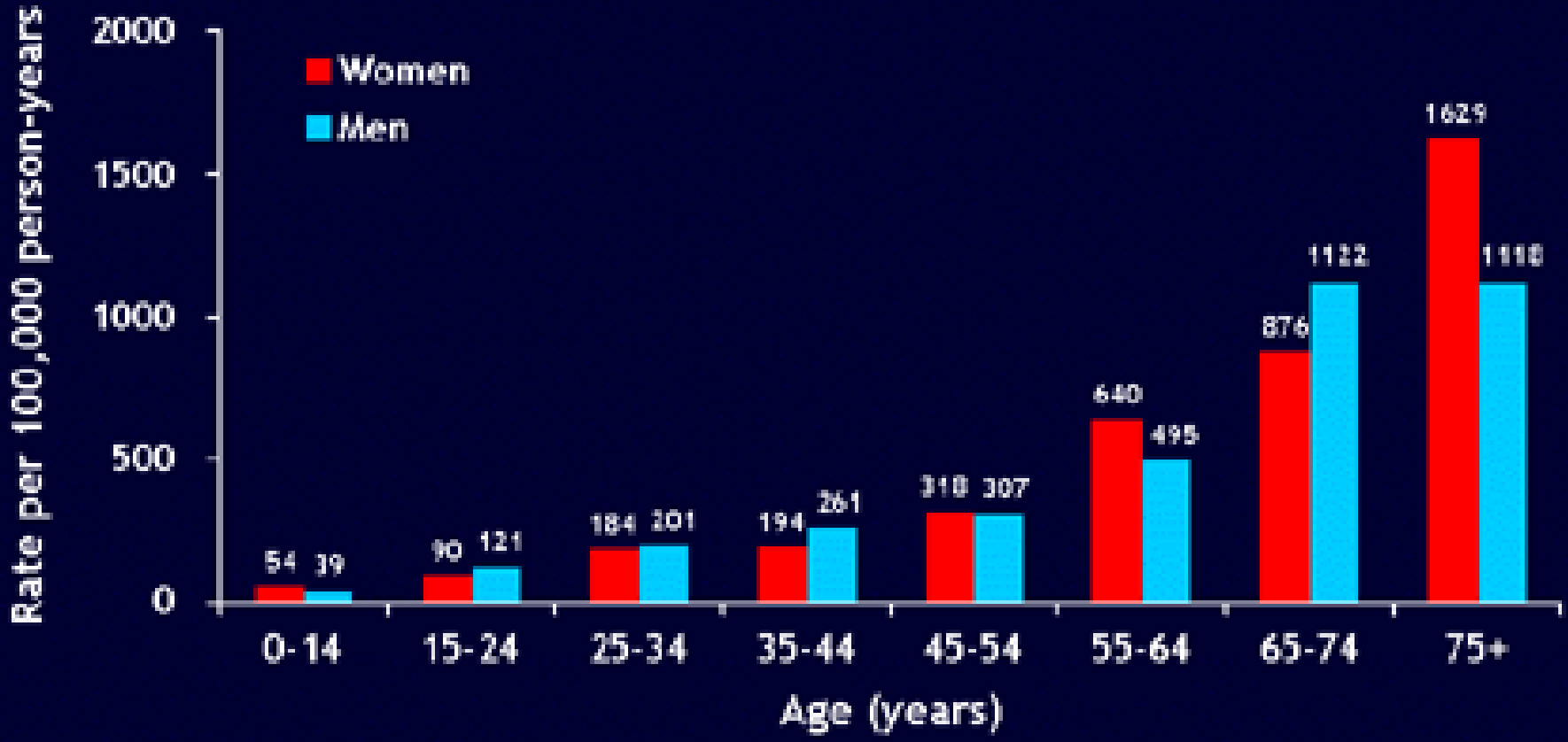
- VARIVAX® licensed 1995
- By 2003: 85% vaccination rate nationwide in population for whom recommended
- Varicella decreased in same period ~ 85% (CDC Varicella Active Surveillance Project)
- Future adult populations in U.S. may rely on vaccination for protection from primary VZV infection

VZV Epidemiology - 2

- Exposure to varicella disease in the community suggested as preventing reactivation of VZV and subsequent HZ and its manifestations.
- From 1999 to 2003, age-standardized rates of overall herpes zoster occurrence increased from 2.77/1,000 to 5.25/1,000 (90%).
- Upward trends in both crude & adjusted rates were highly significant ($p < 0.001$), specifically in the 25–44 year and 65+ year age groups

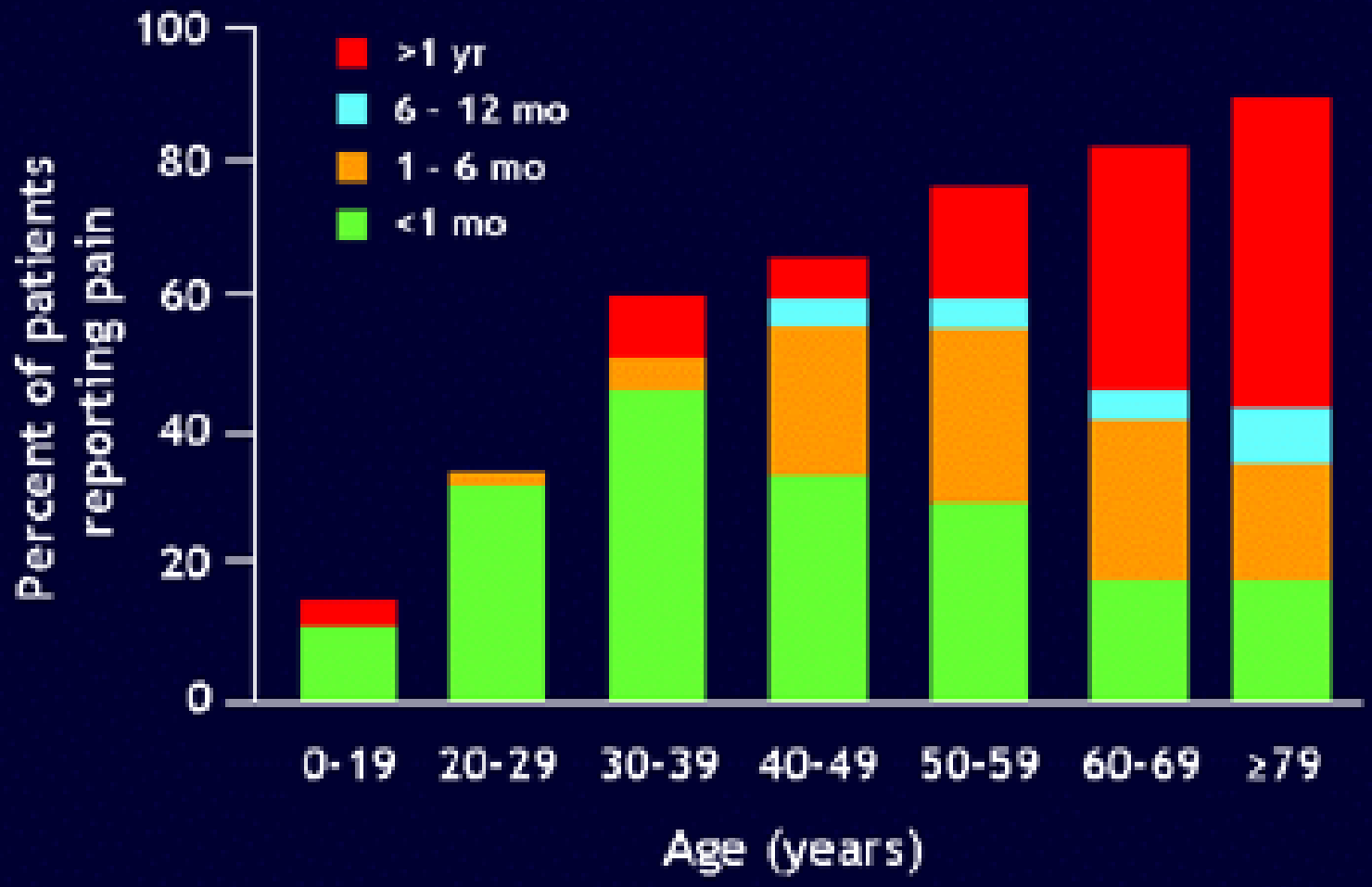
Massachusetts Behavioral Risk Factor Surveillance System
Yih 2005

Incidence of Herpes Zoster Increases With Age



Donahue J et al. *Arch Intern Med* 1995;155:1605-1609.

Prevalence of PHN and Duration of Pain Associated With PHN Increase With Age



Kost R et al. *N Engl J Med* 1998;355:32-42.

ZOSTAVAX™ Clinical Development

1995	VARIVAX™ licensed
02-95	AUC (Brief Pain Inventory) compared to subjective responses in HZ patients published (Lydick)
09-96	ZOSTAVAX™ IND submitted
09-01	Last vaccination (Protocol 004)
11-03	Last HZ case accrued (Protocol 004)
12-03	PHN definition changed from ≥ 30 to ≥ 90 days (Protocol 004)
04-04	Protocol 004 Ended
06-04	Incidence HZ, duration HZ pain & SADLI elevated from tertiary to secondary endpoints; success criteria submitted (Protocol 004)
06-04	Protocol 009 Ended
08-04	Validation of HZ BOI published (Coplan)
04-05	ZOSTAVAX™ BLA submitted

Comparison to Varivax®

	VARIVAX®	ZOSTAVAX™
Disease	Primary Varicella	Herpes Zoster
Dose	1,350 – 17,000 pfu	19,400 – 207,000 pfu
# Doses	12 mos.-12 yrs: 1 optional 2nd dose ≥ 13 years: 2	1

ZOSTAVAX™ Clinical Trials

Protocol	001	002	003	004	005	007	009
Phase	1	2b	2b	3	2b	2a	3
# Subjects	276	398	21	38,546	196	210	698
Age (yrs.)	≥60	≥60	≥30	≥60	≥60	≥ 60	≥ 50
Safety	X	X	X	X	X	X	X
Immuno	X	X	X	X	X	X	
Efficacy				X			
Total Safety Database = 21,000 ZOSTAVAX™ recipients							

ZOSTAVAX™
Protocol 004

Objectives
Protocol 004

Primary

- Reduce incidence/severity HZ and complications in those ≥ 60 yrs. as measured by the Burden of Illness Score (BOI)

- Reduce incidence of PHN

Objectives
Protocol 004

Secondary

- Reduce incidence of HZ
- Reduce duration of HZ pain
- Reduce Activities of Daily Living Interference (ADLI) in subjects w/ HZ

HZ BOI Score
Protocol 004

Zoster Brief Pain Inventory (ZBPI), Coplan 2004

- 121 subjects enrolled w/in 14 days of HZ rash onset
- ZBPI severity-duration associated w/ severity-duration ADLI & worsening QoL
- Score ≥ 3, 90 days or more after HZ rash had high agreement with pain worse than mild using Present Pain Intensity Scale (PPI), modified from the McGill Pain Questionnaire (kappa = 0.72)

Study Design
Protocol 004

- Prospective, randomized, double-blinded, placebo-controlled, multi-center study
- Adults **≥ 60 yrs**
- Randomized 1:1 to vaccine : placebo
- Stratified by age
  - 60-69 yrs. (N =20,747); ≥ 70 yrs. (N =17,799)
- 12 clinical lots
  - 9 accelerated-aged to mimic end-expiry potency

Pertinent Exclusion Criteria
Protocol 004

- More than intermittent use of topical or inhaled corticosteroid
- Life-expectancy < 5 years
- Bed-ridden or homebound
- Cognitive impairment, severe hearing loss (no specific criteria)

ZOSTAVAX™ lots administered

Protocol 004

	Grp 1*	Grp 2**	Grp 3**	Grp 4**
N	835	978	8720	8737
PFU/ Dose (10^3)	50-62	34-42	26-33	21-26
Dates	11/98 11/99	04/99 11/99	07/99 12/00	07/00 09/01
Avg. F/U (days)	1400	1400	1200	900

*Group 1 comprised of 3 unaged clinical lots

**Each group comprised of 3 of the 9 accelerated aged clinical lots

Protocol 004

Randomized 1:1
N = 38,546

ZOSTAVAX™
N = 19,270

Placebo
N = 19,276

Overview of Study Procedures
Protocol 004

Postvaccination		AE Monitoring Substudy	Routine Monitoring Cohort	CMI Substudy
VRC	D 0-42	X		
ATRS Safety	D 42	X	X	X
ATRS HZ	Monthly thru study end	X Hospitalization	X	X
Immuno	D 1, W 6, M 12, 24, 36			X
Following HZ rash		All Subjects		
Immuno	D 1, W 3 & 6	X		
IZIQ, ZBPI	D 0-182	X		

ATRS: Automated Telephone Response System

Population for Analysis
Protocol 004

- ITT – all randomized
  - Evaluable HZ by PCR, culture, CEC; safety
- MITT (modified ITT)
  - **Primary efficacy analyses**
  - Followed ≥ 30 days postvaccination
  - Did not develop evaluable HZ w/in 30 days
  - Evaluable HZ per hierachical testing (PCR, culture, CEC determination)
- MITT2
  - MITT, but evaluable HZ per Clinical Evaluation Committee (CEC)

Results
Protocol 004

Demographics

Protocol 004

	ZOSTAVAX™	Placebo
Male	59.2%	58.9%
Female	40.8%	41.1%
Black	2.0%	2.2%
Hispanic	1.4%	1.3%
White	95.4%	95.4%
Other	1.1%	1.2%
Mean Age	69.4 yrs.	69.4 yrs.
Age Range	60-99	59-94

Disposition

Protocol 004

	ZOSTAVAX™	Placebo
Enrolled	19,270	19,276
Completed	18,359 (95.3%)	18,357 (95.2%)
Died	793 (4.1%)	792 (4.1%)
Withdrawn	57 (0.3%)	75 (0.4%)
Lost to follow- up	53 (0.3%)	40 (0.2%)

Hierarchical HZ Determination

Protocol 004

- PCR + or –
  - 93.4% (894/957) of evaluable HZ cases
  - Wild type VZV, Oka/Merck attenuated VZV, HSV
  - No Oka/Merck VZV isolated from lesions
  - If +VZV and +HSV, determined by CEC (1 case)
- Viral Culture +
  - 1.0% (10/957) of evaluable HZ cases
  - VZV, HSV
- CEC Adjudication
  - 5.5% (53/957) of evaluable HZ cases
  - Determination if not diagnosed by PCR or culture
  - All HZ cases reviewed by Clinical Evaluation Committee

"Co-Primary" Endpoint – 1

Protocol 004

Decrease in HZ Burden-of-Illness (BOI)

61.1% (51.1, 69.1)

Mean sum of areas under curve

$\leq$ 6 months in HZ cases

X

Proportion of subjects with HZ

in treatment arm

Success Criteria: point estimate > 47%; LL 95% CI > 25%

"Co-Primary" Endpoints – 2

Protocol 004

Decrease in Incidence of PHN

66.5% (47.5, 79.2)

- Pain ≥ 3 (0-10 point scale, 10 = worst pain)
- Occurring/persisting 90 days after HZ onset
- 30 day cutoff changed after last HZ case accrued

Success Criteria: point estimate > 62%; LL 95% CI > 25%

Secondary Endpoint - 1

Protocol 004

Decrease in Incidence HZ

51.3% (44.2. 57.6)

Elevated to secondary endpoint after last HZ case accrued but prior to formal unblinding

Success Criteria: LL 95% CI > 25%

Secondary Endpoint – 2
Protocol 004

Duration of clinically significant pain 20 days (vaccine) vs. 22 days (placebo)

- Clinically significant = pain score ≥ 3, 0-10 pt. scale
- P-value < 0.001 (MITT)
- P-value = 0.041 (Evaluable HZ cases only)
- Elevated to secondary endpoint after last HZ case accrued but prior to formal unblinding

Success Criteria: p-value < 0.001

Secondary Endpoint – 3
Protocol 004

Substantial Interference with Activities of Daily Living (SADLI)

"Because Substantial ADLI can only occur among HZ cases, the benefit of vaccination in reducing the incidence of Substantial ADLI was confounded by the benefit of vaccination in reducing HZ incidence."

(Clinical Study Report, page 108)

Secondary Endpoint – 4

Protocol 004

Substantial Interference with Activities of Daily Living (SADLI)

- Combined ADLI score ≥2 for ≥7 days
- 36.2% (ZOSTAVAX) vs. 39.4% (Placebo)
- 8.2% (-9.4, 22.9) in ZOSTAVAX group beyond the reduction in HZ incidence
- P-value = 0.341
- Does not include vaccine effect on HZ incidence, unlike other major endpoints
- Elevated to secondary endpoint after last HZ case accrued but prior to formal unblinding

Success Criteria: p-value 0.05; LL 95% CI > 0

Effect of Covariates on Pain Severity-by-Duration Scores Among Evaluable HZ cases Protocol 004

Parameter	Estimate	Std. Error	P-Value[1]
Vaccine v. Placebo	-35.065	13.909	0.012
Female v. male	-19.691	13.967	0.159
Age (yrs.)	4.665	1.092	<0.001
Antiviral drug use[2]	30.915	20.822	0.138
Analgesic drug use[2]	161.626	16.744	<0.001

1: Based on analysis of covariance (ANCOVA) model; severity-by-duration score of HZ pain = response variable, and listed parameters as explanatory variables.

2: Yes or No, in 6-months following onset HZ rash

p-values (interactions): treatment-by-gender = 0.143;

treatment-by-age = 0.031; treatment-by-antiviral use = 0.381; treatment-by-analgesic use = 0.293

MITT population

Immune Status at HZ Onset

Protocol 004

		ZOSTAVAX™ N = 19,270		Placebo N = 19,276	
# Subjects immunosuppressed at onset of HZ (n)/Total HZ cases (m)		17/320	5.3%	16/659	2.4%
		n	%	n	%
	Corticosteroids	5	29.4	6	37.5
	Chemotherapy	4	23.5	6	37.5
	Transplantation	1	5.9	1	6.3
	Malignancy	9	52.9	9	56.3
	Other*	7	41.2	3	18.8

*Includes use of methotrexate, radiation therapy, neoplasm, emphysems, polymyalgia rheumatica, pulmonary fibrosis.

HZ BOI Efficacy by Year

Protocol 004

Yr	ZOSTAVAX™				Placebo				Efficacy (95% CI)
	n	m	F/U	Incid.	n	m	F/U	Incid.	
1	76	19254	19132	0.427	201	19274	19081	2.075	0.79 (0.68, 0.87)
2	103	18994	18827	0.801	194	18915	18679	1.661	0.52 (0.27, 0.68)
3	98	18626	14505	0.809	171	18422	14327	1.482	0.45 (0.19, 0.63)
4	35	9943	5412	0.367	70	9806	5325	1.007	0.64 (0.25, 0.82)
5	3	1906	327	0.094	6	1856	324	0.375	0.75 (0.19, 0.92)

F/U: in person-yrs. Incidence: per 1000 person-yrs

n = # with event in time period m = # followed in time period

PHN Efficacy by Year

Protocol 004

Yr	ZOSTAVAX™				Placebo				Efficacy (95% CI)
	n	m	F/U	Incid.	n	m	F/U	Incid.	
1	5	19254	19132	0.261	33	19274	19081	1.729	0.85 (0.61, 0.95)
2	8	18994	18827	0.425	22	18915	18679	1.178	0.64 (0.16, 0.86)
3	10	18626	14505	0.689	17	18422	14327	1.187	0.42 (-0.34, 0.76)
4	3	9943	5412	0.554	7	9806	5325	1.315	0.58 (-0.85, 0.93)
5	1	1906	327	3.061	1	1856	324	3.083	0.007 (-76.93, 0.99)

F/U: in person-yrs. Incidence: per 1000 person-yrs

n = # with event in time period m = # followed in time period

HZ Efficacy by Year

Protocol 004

Yr	ZOSTAVAX™				Placebo				Efficacy (95% CI)
	n	m	F/U	Incid.	n	m	F/U	Incid.	
1	76	19254	19132	3.972	201	19274	19081	10.534	0.62 (0.51, 0.71)
2	103	18994	18827	5.471	194	18915	18679	10.386	0.47 (0.33, 0.59)
3	98	18626	14505	6/756	171	18422	14327	11.936	0.43 (0.27, 0.56)
4	35	9943	5412	6.467	70	9806	5325	13.145	0.51 (0.25, 0.68)
5	3	1906	327	9.183	6	1856	324	18.500	0.50 (-1.32, 0.92)

F/U: in person-yrs. Incidence: per 1000 person-yrs

n = # with event in time period m = # followed in time period

Mean Worst HZ Pain (ITT)

Protocol 004

	ZOSTAVAX™ (95% CI)	Placebo (95% CI)
D 1 (rash onset)	3.6 (2.5, 4.8)	5.0 (4.3, 5.7)
D 2	4.1 (3.3, 4.8)	4.3 (3.8, 4.7)
D 3	4.3 (3.7, 4.8)	4.2 (3.8, 4.7)
D 4-5	4.6 (4.2, 5.0)	4.3 (4.1, 4.6)
D 9-11	3.6 (3.2, 4.0)	3.6 (3.4, 3.8)
Wk 4	1.9 (1.5, 2.2)	2.0 (1.8, 2.2)
Wk 6	1.2 (0.9, 1.4)	1.3 (1.1, 1.5)
Wk 8	0.8 (0.6, 1.0)	1.1 (0.9, 1.3)
Wk 12	0.5 (0.4, 0.7)	0.8 (0.6, 0.9)
Wk 16	0.4 (0.2, 0.5)	0.6 (0.4, 0.7)
Wk 26	0.2 (0.1, 0.2)	0.4 (0.3, 0.5)

Effect of Age on Efficacy

Protocol 004

		Efficacy (95% CI)
BOI	60-69 yrs.	0.655 (0.515, 0.755)
	≥ 70 yrs.	0.554 (0.399, 0.669)
Incidence PHN	60-69 yrs.	0.656 (0.204, 0.867)
	≥ 70 yrs.	0.668 (0.433, 0.813)
Incidence HZ	60-69 yrs.	0.639 (0.555, 0.709)
	≥ 70 yrs.	0.376 (0.250, 0.481)

Vaccine Efficacy on HZ Incidence by Age

FDA exploratory analysis - Protocol 004

Age (Yrs.)	Incidence rate / 1000 person yrs. (# HZ cases / # subjects in age group)		Vaccine Efficacy (HZ)
	ZOSTAVAX™	Placebo	
59-64	3.441 (54/5216)	9.945 (153/5198)	0.654 (0.528, 0.746)
65-69	4.351 (68/5154)	11.626 (181/5158)	0.626 (0.506, 0.717)
70-74	6.435 (89/4545)	11.438 (158/4560)	0.437 (0.271, 0.566)
75-79	7.182 (67/3076)	11.312 (103/2999)	0.360 (0.129, 0.530)
80-84	9.773 (31/1063)	12.230 (39/1097)	0.201 (-0.281, 0.501)
85-89	10.040 (5/181)	11.570 (7/210)	0.132 (-1.734, 0.725)
90+	19.608 (1/19)	14.286 (1/25)	-0.373 (-20.945, 0.91.4)

Vaccine Efficacy Above and Beyond VE_{HZ}

FDA Exploratory Analyses - Protocol 004

- Median HZ BOI among HZ cases
  - 82.50 (ZOSTAVAX)
  - 87.75 (Placebo)

  P-value (Wilcoxon) = 0.25
- Percent of HZ cases with PHN
  - 8.57% (ZOSTAVAX)
  - 12.5% (Placebo)

  P-value (Fisher) = 0.08
- Duration of clinically significant pain (days)
  - 19 (ZOSTAVAX)
  - 22 (Placebo)

  P-value (Wilcoxon) = 0.09

Comparison of distributions of BOI between Placebo and ZOSTAVAX group among HZ cases

FDA Exploratory Analysis- Protocol 004

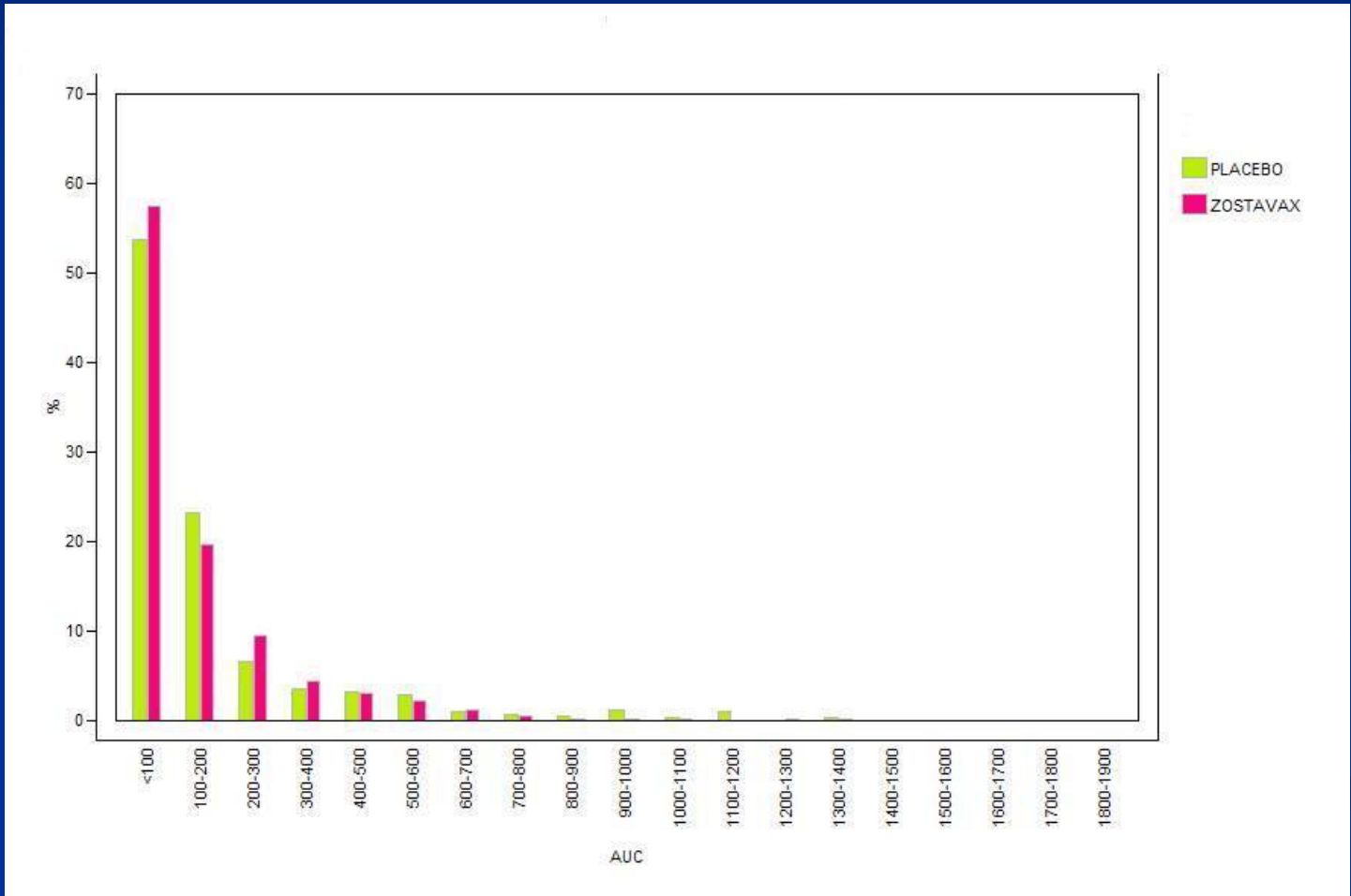


Table 3. Comparison of BOI between Vaccine and Placebo Groups

	Zoster vaccine	Placebo	
# subjects	19254	19247	
# HZ cases	315	642	
Total follow-up time (yrs)	58203	57736	
mean follow-up per subject (yrs)	3.02	3.00	
HZ incidence rate Per 1000 person-yrs	5.41	11.12	VE_{HZ} = 51.3% (44.3%, 57.4%)
HZ incidence rate (crude rate)	1.64%	3.34%	VE_{HZ} = 51.0% (44.0%, 57.1%)
Sum of HZ BOI	46341	114057	
mean HZ BOI per HZ case	147.1	177.7	
median HZ BOI *among HZ cases*	**82.50**	**87.75**	**p-value (Wilcoxon) = 0.25**
mean HZ BOI *per subject*	2.41	5.93	VE_{BOI} = 61.1% (51.1%, 69.1%)

FDA Exploratory Analysis – Protocol 004

Comparison of BOI between Placebo and Zostavax group among HZ cases

FDA Exploratory Analysis – Protocol 004

Test	p-value	p-value(age-adjusted)
Log-Rank	0.0863	0.0330
Wilcoxon	0.2460	0.0985
Tarone	0.1848	0.0679
Peto	0.2530	0.1083
Modified Peto	0.2535	0.1088
Fleming(ρ=1)	0.2460	0.1064
Kolmogorov-Smirnov	0.7907	

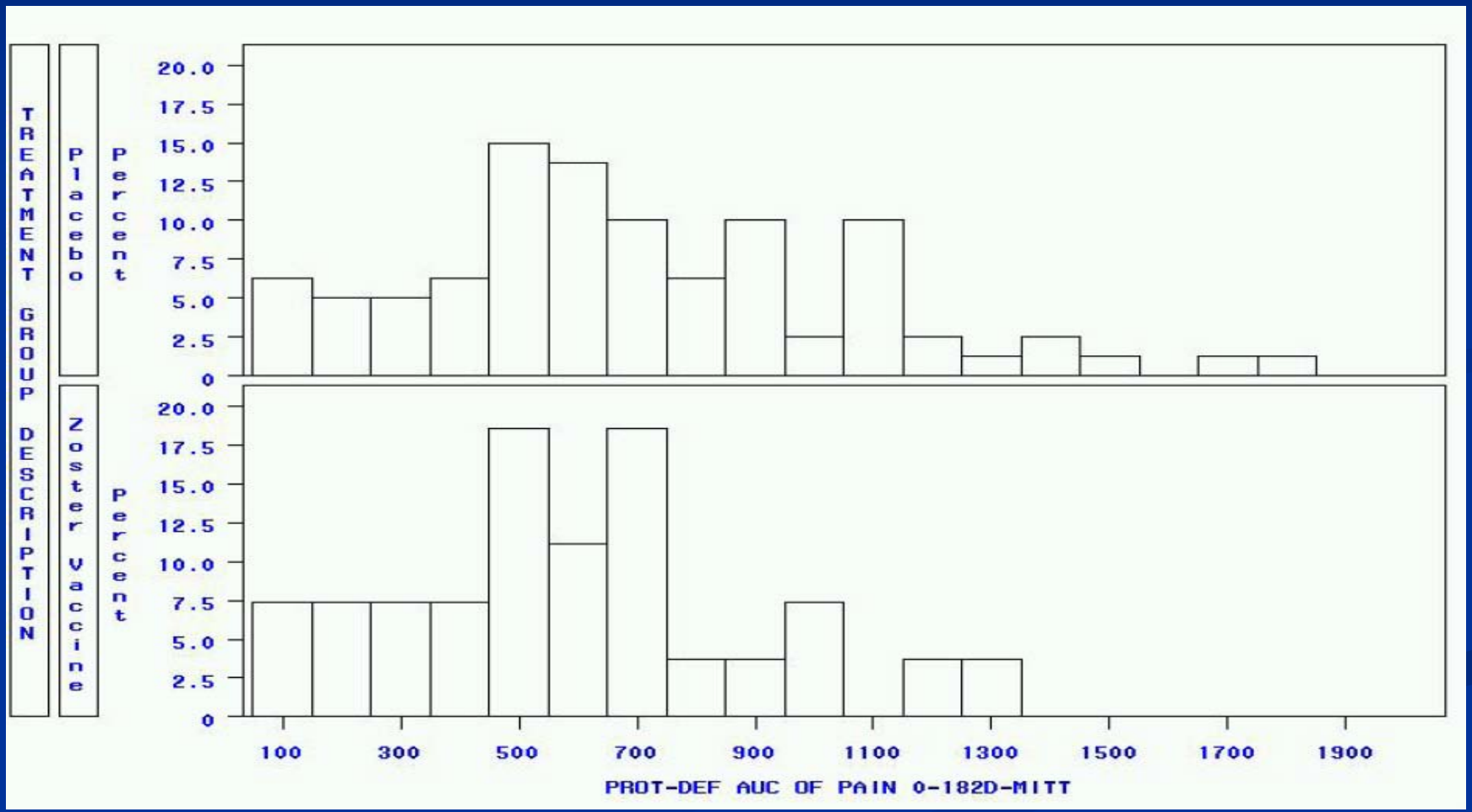
Table 4. Comparison of PHN Incidence between Vaccine and Placebo Groups

	Zoster vaccine	Placebo	
# subjects	19254	19247	
# HZ cases	315	642	
Total follow-up time (yrs)	58203	57736	
mean follow-up per subjects (yrs)	3.02	3.00	
# PHN cases	27	80	
percent of PHN among HZ cases	**8.57%**	**12.5%**	**p-value (Fisher) = 0.08**
PHN incidence rate per1000 person-yrs	0.464	1.384	VE_{PHN} = 66.5% (48.4%, 78.3%)

FDA Exploratory Analysis – Protocol 004

Comparison of distributions of BOI between Placebo and ZOSTAVAX group among PHN cases

FDA Exploratory Analysis – Protocol 004



Comparison of BOI among PHN cases
FDA Exploratory Analysis – Protocol 004

	Zoster vaccine	Placebo	
mean HZ BOI per PHN case	580.5	700.2	
median HZ BOI *among PHNcases*	553	612	p-value (Wilcoxon) = 0.15

Comparison of BOI between Placebo and Zostavax group among PHN cases

FDA Exploratory Analysis – Protocol 004

Test	p-value	p-value(age-adjusted)
Log-Rank	0.1138	0.1019
Wilcoxon	0.1486	0.1593
Tarone	0.1262	0.1153
Peto	0.1482	0.1449
Modified Peto	0.1493	0.1468
Fleming(ρ=1)	0.1486	0.1415
Kolmogorov-Smirnov	0.4579	

Immunogenicity

Immunogenicity Assays
Protocol 004

- gpELISA
- Responder Cell Frequency (RCF)
- IFN-γ ELISPOT

gpELISA Fold Rise 6 wks postvaccination

Protocol 004

Clinical Lot*	GMF (95% CI)
1562W-E471	1.7 (1.5, 2.0)
1563W-E472	1.8 (1.5, 2.1)
1564W-E473	1.9 (1.6, 2.3)
1588W-G479	1.7 (1.5, 1.9)
1589W-G480	1.6 (1.4, 1.8)
15990W-G481	1.6 (1.4, 1.8)

* Accelerated aged lots

gpELISA by HZ Status
Protocol 004

		ZOSTAVAX	Placebo
GMT (6wk) gpELISA units/mL	HZ	272 (162, 457) N = 9	182 (134, 247) N = 23
	No HZ	478 (445, 515) N = 658	296 (273, 321) N = 661
GMFR D 0 – Wk 6	HZ	1.1 (0.9, 1.4) N = 9	0.9 (0.8, 1.1) N = 23
	No HZ	1.7 (1.6, 1.8) N = 646	1.0 (1.0, 1.0) N = 650

HZ Risk by 6 Wk gpELISA Titer

FDA Exploratory Analysis - Protocol 004

gpELISA	ZOSTAVAX™		Placebo	
gpELISA u/mL	n/N	%	n/N	%
≤100	0/24	0%	5/92	5.43%
100 - ≤ 200	3/86	3.49%	6/147	4.08%
200 - ≤ 300	3/108	2.78%	5/118	4.24%
300 - ≤ 400	1/121	0.83%	6/111	5.41%
400 - ≤ 500	1/18	5.56%	0/14	0%
500 - ≤ 600	0/31	0%	0/32	0%
600 - ≤ 700	0/34	0%	1/16	6.25%
700 - ≤ 800	0/35	0%	0/20	0%
800 - ≤ 900	0/29	0%	0/17	0%
900 - ≤ 1000	0/23	0%	0/12	0%
> 1000	1/146	0.68%	0/94	0%

N = # subjects in group w/given titer

n = # subjects in group developing HZ

Herpes Zoster
Protocol 004

- No clear difference in rates of various reported complications among HZ cases in the treatment groups
- HZ associated w/immunosuppression
  - Number of immunosuppressed subjects w/HZ in each treatment group was equal
- 2 placebo subjects & 1 ZOSTAVAX subject developed multiple evaluable cases of HZ (only data from 1st case used in analyses)

gpELISA: ZOSTAVAX vs. Naturally Occurring HZ

Protocol 004

	Following receipt of ZOSTAVAX™	Naturally Occurring HZ following:	
		ZOSTAVAX™	Placebo
After →	Vaccination	Rash Onset	Rash Onset
GMT 6wk	475 (442, 511)	2042 (1805, 2309)	2260 (2070, 2467)
GMFR D 0 – 6 wk	1.7 (1.6, 1.8)	3.2 (2.6, 3.9)	3.1 (2.7, 3.5)

Safety

Protocol 004

Randomized 1:1

N = 38,546

ZOSTAVAX™	Placebo
N = 19,270	N = 19,276
↓	↓
AE Monitoring Substudy	AE Monitoring Substudy
N = 3,345	N = 3,271
OR	OR
Routine Monitoring Cohort	Routine Monitoring Cohort
N = 15,925	N = 16,006
CMI Substudy	CMI Substudy
N = 691	N = 704

Safety Monitoring – 1

Protocol 004

AE Substudy (N = 6,616)

- Vaccine Report Cards
  - Solicited local AEs Days 0-4
  - Temperature Days 0-21
  - Rashes, other complaints, illness Days 0-42
- Automated Telephone Response System (ATRS)
  - Day 42 Safety specific follow-up
    - Rash, unusual reactions, hospitalizations, disability, life-threatening events, new diagnosis of cancer, overdose of any medication
  - Monthly for suspected HZ, hospitalization
  - Medical record review on or around Day 42 (AEs, HZ)

Safety Monitoring – 2

Protocol 004

Routine Monitoring Cohort (N = 31,930)

- ATRS Day 42 Safety Follow-up
  - Rash, unusual reactions, hospitalizations, disability, life-threatening events, new diagnosis of cancer, overdose of any medication
- Available Medical record review ~ Day 42
  - AEs
  - HZ
- Otherwise safety monitoring – passive
  (Monthly ATRS monitored for suspected HZ)

ATRS 42 Day Safety Follow-Up By Subject - Protocol 004

	N	%
Total Population - Protocol 004	38,546	100%
Subjects in Day 42 ATRS Dataset	25,613	66%
Calls made by subjects per protocol	21,117	55%
Calls made by staff for subjects	4,496	11%

ATRS 42 Day Safety Follow-Up - 2

- 601 of 6616 subjects (9%) from AE Monitoring Cohort Included in ATRS Day 42 Dataset

- 1,240 additional reports (≥ 6) for subjects after initial entry of their data over ~ 3 year period

ATRS 42 Day Safety Follow-Up Reports by Source and Time - Protocol 004

(includes subjects with multiple entries)

Days Postvaccination	Subject Contact	Staff Called for Subject
-5 – 28	13	2
29-42	10	69
43	15	101
44	17,248	510
45	1,702	207
46	987	137
47	477	137
48	434	87
49	193	131
50	213	112
51-1095	2	4639

AE Rates From AE Monitoring Substudy from VRC Days 0-42 - Protocol 004

	ZOSTAVAX	Placebo
Number of subjects with VRCs	3345	3271
Solicited AEs		
Temperature ≥ 38.3°C	0.8%	0.9%
Temperature "abnormal" but < 38.3°C	7.2%	6.0%
Erythema*	36%	7%
Pain/Tenderness*	35%	9%
Swelling*	26%	4.5%
Unsolicited AEs		
Pruritis	7%	1%
Warmth	1.7%	0.3%

*Specifically queried on VRC; all had p-value for risk difference < 0.001

Abnormal temperature = qualitatively abnormal

Systemic AEs (> 1%)
AE Monitoring Substudy
Days 0 – 42 Protocol 004

	ZOSTAVAX™	Placebo
Subjects w/ follow-up	3326	3249
Cardiovascular	1.2%	1.2%
Digestive	3.7%	3.8%
General body	10.5%	9.8%
Headache	2.7%	2.6%
Musculoskeletal	1.4%	1.2%
Nervous System	1.7%	1.8%
Respiratory	7.2%	6.2%
Respiratory disorder	2.0%	1.7%
Respiratory infection	1.1%	0.8%
Skin	7.6%	7.3%

Serious Adverse Event Rates Days 0-42 - Protocol 004

		ZOSTAVAX™	Placebo
Routine Monitoring Cohort N = 31,930	SAE	1.24% N = 191	1.38% N = 213
AE Monitoring Substudy N = 6,616	SAE	1.92% N = 64	1.26% N = 41
AE Monitoring Substudy 60-69 yrs. N = 3,459	SAE	1.27% N = 22	1.05% N = 18
AE Monitoring Substudy ≥ 70 yrs. N = 3,157	SAE	2.63% N = 42	1.49% N = 23
Overall Study N = 38,546	Death*	N = 14	N = 16

Deaths* Resulting in SAEs Days 0-42

Protocol 004	Number of Events	
	ZOSTAVAX™ N = 19,270	Placebo N = 19,276
All SAEs resulting in death	14	16
Myocardial infarction	7	5
Cardiovascular Dz.	2	0
Heart arrest	0	2
Heart failure	1	0
Sudden death	0	1
Cerebrovascular accident	2	1
Carcinoma	2	4
Aspiration pneumonia	0	1
Gangrene, intestinal	0	1
Liver failure	0	1

*26 of 30 deaths reported from Routine Monitoring Cohort

Hospitalization: Day 0 - Study End AE Monitoring Substudy Protocol 004

	ZOSTAVAX™ N = 3345		Placebo N = 3271	
	n/m	Rate/ 1000 pt.- yrs. (95% CI)	n/m	Rate/ 1000 pt.- yrs. (95% CI)
All	1137/3342	107.48 (101.3, 113.9)	1115/3266	107.30 (101.1, 113.8)
HZ-related	5/3342	0.38 (0.12, 0.89)	6/3266	0.47 (0.17, 1.030)

N = # subjects in AE Monitoring Substudy in each treatment group

n = # subjects in category with hospitalization

m = # subjects randomized

No vaccine-related hospitalizations were reported

Deaths Overall: Day 0 – Study End

Protocol 004

	ZOSTAVAX™ N = 19,270		Placebo N = 19,276	
Age (yrs.)	n/m (%)	Death rate / 1000-person yrs. (95% CI)	n/m (%)	Death rate / 1000-person yrs. (95% CI)
60-69	218/10378	6.2 (5.4, 7.08)	246/10369	7.00 (6.15, 7.93)
≥ 70	575/8892	19.08 (17.55, 20.70)	549/8907	18.12 (16.64, 19.70)
All	793/19270	12.14 (11.31, 13.02)	795/19276	12.15 (11.32, 13.02)

n - # subjects in group who died during study

m - # subjects originally randomized to age group

Safety Follow-up
Day 43 – Study End – 1

Protocol 004

- No information on proportion of subjects with ATRS contact at each month, overall, by group and by site. (AE Monitoring Cohort queried for hospitalizations.)
- "Due to the passive and inconsistent nature of safety data collection in the Routine Monitoring Cohort…from Day 43 through study end, caution should be exercised when interpreting these particular data." (Clinical Study Report, p. 309)

AE Monitoring Substudy
AEs > 1%, Day 43 – Study End

	ZOSTAVAX™	Placebo
Subjects w/ follow-up	3342	3271
Cardiovascular	11.0%	11.5%
Digestive	6.4%	5.5%
General Body	9.5%	10.5%
Genitourinary	5.0%	5.6%
Metabolic/nutritional	1.0%	1.3%
Musculoskeletal	6.6%	7.0%
Nervous system	4.5%	4.7%
Respiratory	4.3%	4.7%
Skin	3.1%	3.1%

Protocol 009

Objective - Protocol 009

- Comparison of safety and tolerability profile of a higher potency zoster vaccine with that of a lower potency dose
- Among adults ≥ 50 years of age, the higher potency ZOSTAVAX™ would be generally well tolerated as compared with the lower potency ZOSTAVAX™

Design - Protocol 009

- Double-blind, comparator study
- Randomized 2:1 (high : low potency)
- Subjects ≥ 50 yrs. old
  Stratified: 50-59 yrs. (N = 185)
  ≥ 60 yrs. (N = 513)
- Dose comparison
  58,000 pfu (N = 234) and 207,000 pfu (N = 461)
- 42 Day safety follow-up
  - Vaccine Report Cards
  - Local and systemic AEs
  - Varicella, varicella-like rash
  - HZ, HZ-like rash

Primary Endpoints – Protocol 009

- Difference between higher and lower potency vaccine groups in risk of vaccine-related* serious clinical adverse experiences occurring Day 1 - 42 postvaccination (2-sided, 0.05 level)
- Upper bound of the 95% CI for incidence rate of moderate or severe injection site pain, tenderness, soreness or swelling occurring Day 1 - 5 postvaccination in the higher potency vaccine group be less than 21.5% (historical rate reported with PNEUMOVAX™23).

*Vaccine-related as determined by study investigator

Secondary Endpoints – Protocol 009

- Varicella or varicella-like rash with > 100 lesions Days 1 – 42 postvaccination
- HZ or HZ-like rash Days 1 – 42 postvaccination
- Fever ≥ 38.3°C (oral) Days 1 – 21 postvaccination

Results 1 - Protocol 009

Primary Endpoints

- Vaccine-related* SAEs – No occurrence
- Rate of composite local AEs in high potency group: 17.2% (13.9, 21.0)

  Prespecified criteria: Upper limit of 95% CI < 21.5% based upon PNEUMOVAX™23 historical data

*Vaccine-related as determined by study investigator

Results 2 - Protocol 009

Secondary Endpoints

- Varicella or varicella-like rash (>100 lesions) – no occurrence in either treatment group
- Zoster or zosteriform rash

  3 (0.7) high potency vs. 3 (1.3%) low potency

  p-value: 0.399
- Elevated temperature, ≥38.3 °C

  4 (0.9%) high potency vs. 2 (0.9%) low potency

Safety - 1
SAEs Days 0-42 - Protocol 009

ZOSTAVAX™ High Potency			
Gender	**Age**	**Day of Onset***	**SAE**
Female	66	13	Coronary artery dz.
Male	61	25	Angina pectoris
Female	54	29	Depression
Female	56	41	Enteritis
ZOSTAVAX™ Low Potency			
Gender	**Age**	**Day of Onset**	**SAE**
Male	58	3	Lung cancer

*Number of days postvaccination

Safety - 2
Days 0-42 - Protocol 009

- Deaths: None
- Injection-site reactions composite endpoint:
  17.2% (13.9, 21.0) in high potency group
  9.0% (5.6, 13.1) in low potency group
- Higher rates of injection site reactions in younger subjects more marked in those receiving high potency vaccine: 83% in 50-59 yr. olds vs. 55% in ≥ 60 yr. olds.

Summary of ZOSTAVAX™ Issues

ZOSTAVAX™ Summary - Protocol 004

1. Reduction in HZ incidence: 51% (44, 58) in relatively healthy adults ≥ 60 years old postvaccination; 64% (56, 71) in those 60-69 yrs., but only 38% (25, 48) in those ≥ 70 years.
2. Reduction in PHN incidence: 67% (48, 79) at 90 days following HZ rash onset.
3. Reduction in HZ BOI score: 61% (51, 69) over 6 months following HZ rash onset.
4. Effect on PHN incidence and BOI appears relatively small after accounting for the effect of the vaccine on the incidence of HZ.

ZOSTAVAX™ Summary - Protocol 004

5. In persons with HZ, no clear correlations seen between reduction of BOI scores and measures of clinical benefit, e.g., mortality, serious morbidity, hospitalizations, use of pain medications or interference with ADLs.
6. Completeness of safety, ATRS and study termination follow-up is unclear.
7. Age appears to be the strongest factor determining vaccine effect and in an exploratory analysis, efficacy appears minimal in subjects ~ 75 years and older (the age group with potentially the largest burden of illness).

ZOSTAVAX™ Summary - Protocol 004

7. Relative increase in rate of SAEs seen (D 0-42) in the AE Monitoring Substudy, most notably in subjects aged ≥ 70 years old; however, no specific pattern of SAEs was seen.

8. Exclusion crtieria (not expected to live ≥ 5 more years, not ambulatory, chronic corticosteroid use, cognitive impairment) make it difficult to draw conclusions as to generalizability of the Protocol 004 efficacy and safety analyses to a typical population aged 60 years and older.

ZOSTAVAX™ Summary - Protocol 009

1. Includes younger subjects (50-59 years old) but no comparison of older age strata to previous similar age groups in previous ZOSTAVAX™ studies
2. Vaccine dose 4 times higher than any previously studied, but has no comparison or bridging to previous ZOSTAVAX™ studies
3. Clinical relevance of study endpoints unclear:
   a. Comparison of composite endpoint (local injection-site events) to historical rate in PNEUMOVAX™23
   b. Comparison of investigator-determined, vaccine-related SAEs by dose

Questions for the Committee

Questions for the Committee

1. Are the available data adequate to support the efficacy of ZOSTAVAX™ when administered to individuals ≥ 50 years of age in:

   a. Preventing herpes zoster?

   b. Preventing post-herpetic neuralgia? Preventing post-herpetic neuralgia beyond the effect on the prevention of herpes zoster?

   c. Decreasing the burden of illness (BOI)? Decreasing the burden of illness (BOI) beyond the effect on the prevention of herpes zoster?

   If not, what additional information should be provided?

Questions for the Committee

2. Are the available data adequate to support the safety of ZOSTAVAX™ when administered to individuals ≥ 50 years of age?

   If not, what additional information should be provided?

Questions for the Committee

3. Please identify any other issues that should be addressed, including post-licensure studies. In particular please address:

   a. Use of the vaccine in persons with co-morbid conditions, e.g., those who might typically reside in assisted living residences and nursing homes.

   b. Use of the vaccine among persons taking chronic immunosuppressive therapies, including corticosteroids.

   c. Use of the vaccine in certain subsets of the sponsor's proposed age indication, e.g., those ≥ 70 years, those ≥ 80 years.

   d. Duration of immunity.

   c. The sponsor's proposed pharmcovigilance plan.

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Acronyms

AE:	Adverse event
ATRS:	Automated telephone response system
BOI:	Burden of illness
CEC:	Clinical evaluation committee
CMI:	Cell-mediated immunity
HSV:	Herpes simplex virus
HZ:	Herpes zoster
ITT:	Intent to treat
IZIQ:	Initial Zoster Impact Questionnaire
MITT:	Modified intent to treat
PFU:	Plaque-forming units
PHN:	Post herpetic neuralgia
PPI:	Present pain intensity scale
QoL:	Quality of life
SADLI:	Substantial interference with activities of daily living
VZV:	Varicella zoster virus
ZBPI:	Zoster brief pain inventory

Additional Slides

Cummulative Incidence of HZ

Protocol 004

Through year	HZ Incidence / 1000 person-yrs.		Efficacy (95% CI)
	ZOSTAVAX™	Placebo	
1	3.970	10.527	62.3% (51.0, 71.0)
2	4.712	10.454	54.9% (46.3, 62.2)
3	5.278	10.862	51.4% (43.9, 57.9)

Determination of HZ

Protocol 004

	ZOSTAVAX		Placebo	
	Evaluable N (%)	Non-Evaluable N (%)	Evaluable N (%)	Non-Evaluable N (%)
Total	316 (67.7)	151 (32.3)	644 (80.6)	155 (19.4)
PCR VZV+	295 (63.2)	---	602 (75.3)	---
PCR VZV --	---	88 (18.8)	---	91 (11.4)
PCR HSV+	---	23 (4.9)	---	21 (2.6)
PCR VZV+ / HSV+	--	--	--	1 (0.1)
Viral Culture VZV+	2 (0.4)	--	8 (1.0)	--
Viral Culture HSV+	--	1 (0.20)	--	--
HZ by CEC early	19 (4.1)	--	34 (4.3)	--
HZ by CEC late	--	3 (0.6)	--	4 (0.5)
Non-HZ by CEC	--	36 (7.7)	--	36 (4.5)

Early: seen during rash stage (crusted vesicles or earlier)

Late: seen beyond crusting stage

Lot Consistency

Protocol 004

- 6 clinical lots, accelerated aged
  - Paired clinical lots derived from same parental lot
  - Data pooled from each pair of aged lots
- Clinical EPs
  - HZ BOI
  - Incidence of PHN
  - Incidence of HZ
- No apparent differences reported by sponsor
- Relatively wide CI for incidence of PHN due to few cases per clinical lot.